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Columns: REVIEW

Hepatitis C genotype 4: The past, present, and future

Abdel-Ghaffar et al. HCV-GT-4: Past to Future

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Reviewer 1:

Comment 1:

Simeprevir is traditionally Geno Specific G1a,b here it is said pangenomic needs references.

Response 1:

Recently, DAAs with pan-genotypic activities simeprevir, sofosbuvir and daclatasvir have been recommended in triple regimens with PEG-IFN/ribavirin for the treatment of HCV genotypes 4[1]. Simeprevir is active against genotypes 1, 2, 4, 5 and 6. It is administered as a once-daily tablet orally and has demonstrated a favorable safety profile and limited drug-drug interactions [2]. RESTORE, a phase III, multicenter, single-arm, open-label study, conducted in France and Belgium, evaluated simeprevir (150 mg once-daily for 12 wk in combination with PegIFN/RBV, followed by 12-36 wk of PegIFN/RBV only) in 107 patients with HCV 4, either naïve or treatment-experienced [3]. Recent European guidelines have included a 24-48 wk simeprevir plus PEG-IFN/RBV combination as an option for HCV 4-related compensated liver disease (including cirrhotics), suggesting interruption of treatment if HCV-RNA levels are ≥ 25 IU/mL at week 4, 12 or 24[4].

Information was added to clarify this point in the first paragraph (Page: 27), lines: 4-15, with addition of 3 new references.

Reviewer 2:

Comment 1:

1. The authors should describe the predictive factors such as vital mutations regarding peg-INF/RBV therapy, although they described IL28B as a predictive factor. The authors could refer to the following references. Example; ① Kim SR, El Shamy A, Imoto S, et al: Prediction of response to pegylated interferon/ribavirin combination therapy for chronic hepatitis C genotype 1b and high viral load. J Gastroenterol 2012; 47: 1143-51. ② Enomoto N, Sakuma I, Asahina Y, et al: Mutations in the nonstructural protein 5A gene and response to interferon in patients with chronic hepatitis C virus 1b infection. N Engl J Med 1996; 334: 77-81. ③ El Shamy A, Nagano Fujii M, Sasase N, et al: Sequence variation in hepatitis C virus nonstructural protein 5A predicts clinical outcome of pegylated interferon/ribavirin combination therapy. Hepatology. 2008; 48: 38-47. ④ Akuta N, Suzuki F, Kawamura Y, et al: Predictive factors of early and sustained responses to peginterferon plus ribavirin combination therapy in Japanese patients infected with hepatitis C virus genotype 1b: amino acid substitutions in the core region and low-density lipoprotein cholesterol levels. J Hepatol 2007; 46: 403-10.

Response 1:

Mutations in the NS5A region, particularly in patients with more than 6 aa mutations in the IRRDR (Interferon Ribavirin resistance – determining region) are strongly associated with the therapeutic response to PEG-IFN and ribavirin combination therapy, whereas a less diverse (≤ 5) IRRDR sequence predicts non- SVR [5-7].

Information was added in the first paragraph (Page 21), lines: 11-14, with addition of 3 references

Comment 2:

2. The authors should add a severe adverse effect including cardiac arrest concerning DDA combination therapy. The authors could refer to the following references. Example; ①Mizokami M, Yokosuka O, Takehara T, et al: Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. Lancet Infect Dis. 2015 Jun; 15(6): 645-653.

Response 2:

The most common and tolerable adverse effects of DAA combination therapy are nasopharyngitis, headache and malaise [8]. However The FDA warned on March 2015 that serious slowing of the heart rate can occur when the antiarrhythmic drug amiodarone is taken together with either Harvoni (ledipasvir/sofosbuvir) or with SOF taken in combination with another direct acting antiviral for the treatment of hepatitis C infection. They recommended that health care professionals should not prescribe either Harvoni or SOF combined with another direct acting antiviral, such as daclatasvir or Olysio (simeprevir), with amiodarone [9].

Information was added in the last paragraph (Page 32), lines: 12-19, with addition of 2 references

Comment 3:

Minor points: 1.The authors should describe adverse effects such as rash including Stevens-Johnson syndrome in telaprevir + peg-IFN + ribavirin treatment.

Response 3:

Telaprevir may cause skin rash, in up to 5%ofcases it can be severe, and it may cause Stevens-Johnson Syndrome (SJS) [10]. On December 2012; FDA Drug Safety Communication reported serious skin reactions after

combination treatment with the Hepatitis C drugs Incivek (telaprevir), PEG-IFN alfa, and ribavirin. These types of skin reactions (toxic epidermal necrolysis (or TEN), drug rash with eosinophilia and systemic symptoms , and SJS) may be considered different varieties along a spectrum of serious skin reactions and can be difficult to tell apart from each other. FDA added a boxed warning to the Incivek drug label stating that Incivek combination treatment must be immediately stopped in patients experiencing a rash with systemic symptoms or a progressive severe rash [11].

Information was added in the second paragraph (Page 26), lines: 13-20, with addition of 2 references:

References

1 Papastergiou V, Karatapanis S. Current status and emerging challenges in the treatment of hepatitis C virus genotypes 4 to 6. *World journal of clinical cases* 2015; **3**(3): 210-220 [PMID: 25789294 PMCID: 4360493 DOI: 10.12998/wjcc.v3.i3.210[

2 Gaetano JN .Benefit-risk assessment of new and emerging treatments for hepatitis C: focus on simeprevir and sofosbuvir. *Drug, healthcare and patient safety* 2014; **6**: 37-45 [PMID: 24729731 PMCID: 3976205 DOI: 10.2147/DHPS.S43304[

3 Moreno C, Hezode C, Marcellin P, Bourgeois S, Francque S, Samuel D, Zoulim F, Grange JD, Lenz O, Ouwerkerk-Mahadevan S, Peeters M, Beumont-Mauviel M, Jessner W. P1319 ONCE-DAILY SIMEPREVIR (TMC435) WITH PEGINTERFERON/RIBAVIRIN IN TREATMENT-NAIVE OR TREATMENT-EXPERIENCED CHRONIC HCV GENOTYPE-4 INFECTED PATIENTS: FINAL RESULTS OF A PHASE III TRIAL. *Journal of hepatology* 2014; **60**(1): S535 [DOI: 10.1016/s0168-8278(14)61486-0[

4 Poordad F, McCone J, Jr., Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, Reddy KR, Goodman ZD, Boparai N, DiNubile MJ, Sniukiene V, Brass CA, Albrecht JK, Bronowicki JP. Boceprevir for untreated chronic HCV genotype 1 infection. *The New England journal of medicine* 2011; **364**(13): 1195-1206 [PMID: 21449783 PMCID: 3766849 DOI: 10.1056/NEJMoa1010494[

5 Kim SR, El-Shamy A, Imoto S, Kim KI, Ide YH, Deng L, Shoji I, Tanaka Y, Hasegawa Y, Ota M, Hotta H. Prediction of response to pegylated interferon/ribavirin combination therapy for chronic hepatitis C genotype 1b and high viral load. *Journal of gastroenterology* 2012; **4** :(10)7] 1151-1143PMID: 22441534 DOI: 10.1007/s00535-012-0578-z[

6 El-Shamy A, Nagano-Fujii M, Sasase N, Imoto S, Kim SR, Hotta H. Sequence variation in hepatitis C virus nonstructural protein 5A predicts clinical outcome of pegylated interferon/ribavirin combination therapy. *Hepatology* 2008; **48**(1): 38-47 [PMID: 18537193 DOI: 10.1002/hep.22339[

7 Yano Y, Seo Y, Miki A, Saito M, Kato H, Hamano K, Oya M, Ouchi S, Fujisawa T, Yamada H, Yamashita Y, Tani S, Hirohata S, Yoon S, Kitajima N, Kitagaki K, Kawara A, Nakashima T, Yu H, Maeda T, Azuma T, El-Shamy A, Hotta H, Hayashi Y. Mutations in non-structural 5A and rapid viral response to pegylated interferon-alpha-2b plus ribavirin therapy are associated with therapeutic efficacy in patients with genotype 1b chronic hepatitis C. *International journal of molecular medicine* 2012; **30**(5): 1048-1052 [PMID: 22899224 DOI: 10.3892/ijmm.2012.1093[

8 Mizokami M, Yokosuka O, Takehara T, Sakamoto N, Korenaga M, Mochizuki H, Nakane K, Enomoto H, Ikeda F, Yanase M, Toyoda H, Genda T, Umemura T, Yatsuhashi H, Ide T, Toda N, Nirei K, Ueno Y, Nishigaki Y, Betular J, Gao B, Ishizaki A, Omote M, Mo H, Garrison K, Pang PS, Knox SJ, Symonds WT, McHutchison JG, Izumi N, Omata M. Ledipasvir and sofosbuvir fixed-dose combination with and without

ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. *The Lancet Infectious diseases* 2015; **15**(6): 645-653 [PMID: 25863559 DOI: 10.1016/S147-70099(15)3099-3X[

9 Hepatitis C Treatments Containing Sofosbuvir in Combination With Another Direct Acting Antiviral Drug: Drug Safety Communication - Serious Slowing of Heart Rate When Used With Antiarrhythmic Drug Amiodarone. 2015. Available from: URL : http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm439662.htm

10 Pellicer Corbí M, Matoses Asensio S, Garcia Muñoz C, Ortiz Campos M, Herranz Muñoz C, Fernandez-Pacheco M, Garcia-Valdecasas, Luque Infantes M. PS-071Telaprevir-induced Stevens-Johnson Syndrome. A case report. *European Journal of Hospital Pharmacy: Science and Practice* 2014; **21**(Suppl 1): A172-A173 [DOI: 10.1136/ejhpharm-2013-000436.422[

11 FDA Drug Safety Communication: Serious skin reactions after combination treatment with the Hepatitis C drugs Incivek (telaprevir), peginterferon alfa, and ribavirin. 2012. Available from: URL: http://www.fda.gov/Drugs/DrugSafety/ucm332731.htm

Answer to chief editor:

We had change ref 201.

Thank you!